REVIEW

Meta-analysis of studies on individual consumption of chlorinated drinking water and bladder cancer

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Study objective: To evaluate whether consumption of chlorinated drinking water is associated with bladder cancer.
Design: A bibliographic search was conducted and the authors selected studies evaluating individual consumption of chlorinated drinking water and bladder cancer. The authors extracted from each study risk estimates for intermediate and long term (>40 years) consumption of chlorinated water, stratified by sex when possible, and performed meta-analysis for the two exposure levels. A meta-analysis was also performed of the dose-response regression slopes.
Setting: Populations in Europe and North America.
Participants: Those included in six case-control studies (6084 incident bladder cancer cases, 10 816 controls) and two cohort studies (124 incident bladder cancer cases) fulfilling the inclusion criteria.
Main results: Ever consumption of chlorinated drinking water was associated with an increased risk of bladder cancer in men (combined OR=1.4, 95%CI 1.1 to 1.9) and women (combined OR=1.2, 95%CI 0.7 to 1.8). The combined OR for mid-term exposure in both genders was 1.1 (95% CI 1.0 to 1.2) and for long term exposure was 1.4 (95%CI 1.2 to 1.7). The combined estimate of the slope for a linear increase in risk was 1.13 (95% CI 1.08 to 1.20) for 20 years and 1.27 (95% CI 1.15 to 1.43) for 40 years of exposure in both sexes.
Conclusions: This meta-analysis of the best available epidemiological evidence indicates that long term consumption of chlorinated drinking water is associated with bladder cancer, particularly in men. The observed relative risk is only moderately high, but the population attributable risk could be important as the vast majority of the population of industrialised countries is potentially exposed to chlorination byproducts for long time periods.

Chlorinated drinking water contains a complex mixture of chlorinated and brominated byproducts with mutagenic and carcinogenic properties. Several toxicological and epidemiological studies have found a positive association between chlorinated drinking water consumption and bladder cancer. An International Agency for Research on Cancer (IARC) working group evaluated the human carcinogenicity for chlorinated drinking water in 1991[1] concluding that there was inadequate evidence for its carcinogenicity to humans (Group 3). This evaluation was based mainly on ecological and death certificate studies. Several epidemiological studies on bladder cancer published after 1991 evaluated individual lifetime consumption to chlorinated drinking water overcoming partially the limitations of earlier studies. All of them found positive associations with bladder cancer. In 1999 the International Agency for Research on Cancer (IARC) re-evaluated individual chlorination byproducts such as chloroform and other trihalomethanes (THM) concluding that there was inadequate evidence for their carcinogenicity.[2] It was argued that although diverse studies had associated chlorinated drinking water intake with cancer, single compounds could not be evaluated as they always occur in mixtures. A more recent report on disinfectant byproducts by the WHO[3] considered that the evidence was insufficient to determine whether observed associations are causal and determine which specific byproducts or other contaminants play a part. Furthermore, it concludes that the health risks from disinfectant byproducts at the levels at which they occur in drinking water are extremely small in comparison with the risks associated to inadequate disinfection. Apart from bladder cancer, other health effects such as colorectal cancer and adverse pregnancy outcomes have also been associated with chlorinated drinking water.[4–6] We performed a meta-analysis of results from epidemiological studies on individual consumption of chlorinated drinking water and bladder cancer following established guidelines.[7] We provide a summary risk estimate of bladder cancer risk associated to chlorinated drinking water exposure, partially overcoming the criticisms raised in international or national evaluations of this risk.

METHODS

Literature search

A systematic bibliographic search was performed looking for studies on bladder cancer and chlorinated drinking water. We focused on those epidemiological studies with accurate exposure assessment—that is, with individual information on long term patterns of water consumption. The availability of residential history obtained from individual interviews linked with water source was defined as the inclusion criterion for the meta-analysis. This inclusion criterion was set because in previous evaluations on disinfection byproducts and cancer by the WHO,[3] the absence of individual information was determined as crucial for the evaluation of cancer risk in humans. According to this criterion, ecological and cancer mortality based studies were excluded. Firstly, we searched in Medline all articles published without using any publication date limit. Search terms included bladder cancer, chlorine, chlorination, trihalomethanes (thm), mx, disinfectant agent, and tap water. The search was performed by consecutively entering single or combination of search terms. The search strategy is summarised as: [(chlorine & bladder cancer) or ((bladder cancer) & (disinfectant agent or chlorination or mx or thm))]. Among the 46 articles identified, 14 were review articles, seven were ecological studies, three were mortality based studies, one discussion, one editorial, one in Russian

Table 1 Description of studies included in the meta-analysis

	Location	Study population	Exposure measurement selected for the meta-analysis	Exposure categories: Referent category	Mid-term exposure	Long term exposure	Confounders considered in the statistical analysis or study designs
Case-control studies			*Duration of exposure to:*				
Cantor *et al* 1998[9]	Iowa (USA)	732 cases 914 population controls	Chlorinated surface water	0 years	1–39 years	⩾40 years	Age, sex, study period, high risk occupation, and cigarettes.
Koivusalo *et al* 1998[8]	Finland	1123 cases 1983 population controls	Substantially mutagenic drinking water	<15 years	15–44 years	⩾45 years	Age, socio economic status and smoking. Results stratified by sex.
King *et al* 1996[10]	Ontario (Canada)	696 cases 1545 population controls	Chlorinated surface water	⩽9 years	10–34 years	⩾35 years	Age, gender, log pack years of smoking, current smoking, education, and calorie intake.
McGeehin *et al* 1993[11]	Colorado (USA)	327 cases 261 other cancer sites controls	Chlorinated water	0 years	1–30 years	>30 years	Coffee consumption, smoking, tap water intake, family history of bladder cancer, sex, and medical history of bladder infection or kidney stones.
Vena *et al* 1993[15]	New York state (USA)	351 cases 855 population controls	Tap water	0–49 years consuming 0–5 glasses/day	0–49 years consuming >10 glasses/day	⩾50 years consuming >10 glasses/day	Age, education, cigarette smoking (pack years), sodium, carotene, and non-tap water. Only men.
Cantor *et al* 1987[13]	USA	2855 cases 5258 population controls	Chlorinated surface water	0 years	1–39 years	⩾40 years	Age, sex, smoking habit, high risk occupation, population size of usual residence and reporting centre.
Cohort studies							
Wilkins and Comstock 1981[14]	Washington County (USA)	31000 study subjects, 81 bladder cancer cases	Drinking water source	Deep well users		Chlorinated surface water users	Age, marital status, education, smoking history, frequency of church attendance, adequacy of housing, and persons per room.
Doyle *et al* 1997[16a] Iowa USA		28237 study subjects, 43 bladder cancer cases	Drinking water source	100% ground water source	Mixed surface-ground water	100% surface water source	Age, education, smoking status, pack years of smoking, physical activity, fruit and vegetable intake, total energy intake, body mass index, and waist to hip ratio

with English abstract not available, 14 were not epidemiological studies on bladder cancer and chlorination (methodological, experimental, or clinical studies), and seven fulfilled our a priori inclusion criteria.[8–14] A second search was performed using bladder cancer and tap water as search terms. From the 25 articles found, only one fulfilled the inclusion criteria.[15] The searches were replicated in Cancerlit and Embase databases. All references retrieved from Cancerlit were included in Medline. One reference found in Embase was not included in Medline.[16] This was a review article in Chinese. The reference lists of the papers selected and the most recent review articles were checked for undetected published studies. A certain number of studies were identified, the studies by Doyle[16a] and Freedman[17] the only ones partially fulfilling the inclusion criteria.

Data

We finally included in the meta-analysis six case-control studies[8–11 13 15] and two cohort studies[14 16a] evaluating individual consumption of drinking water through personal interviews (table 1). The six case-control studies included 6084 incident bladder cancer cases and 10<thin<816 controls. The cohort studies included 124 incident bladder cancer cases (table 1).

The study by Lynch[12] was excluded from the analysis, because although it fulfilled the inclusion criteria, the population study was included in the study by Cantor 1987.[13] The study by Freedman[17] is a case-control study nested in the cohort of the study by Wilkins and Comstock.[14] The study by Freedman, however, evaluated water consumption patterns of the study population only for a limited time period, precisely at the time of the same private census used in the cohort study. We included in the main meta-analysis the cohort study.[14] Although the number of bladder cancer cases was smaller in the cohort study, the exposure assessment was more accurate and closer to the dates in which the study was conducted. The study by Freedman was considered in an alternative analysis. Death certificate based case-control studies,[18–20] although have been frequently quoted, were not included in this meta-analysis because exposure information was either ecological or based on interviews of proxies

Statistical analysis

For each study, odds ratios (OR) or relative risks (RR) and 95% confidence intervals (95% CI) by sex and exposure category were extracted. Two studies provided only gender specific risks[8 14] and overall risk estimates were calculated by us through a meta-analysis of male and female risks. One study included only men[15] and one only women.[16a] We used Wolf's method to combine risk estimates in all meta-analyses. This method is based on the study specific risk estimates and confidence intervals, applying the inverse of variance as the weighting factor.[21] The exposure indices analysed were duration of chlorinated drinking water consumption in the case-control studies and water source in the cohort study. Subjects were classified as whether they ever consumed or not chlorinated drinking water. When not presented in the original papers, combined risk estimates for ever-consumers were estimated through a meta-analysis of published risk estimates for exposed subcategories. Those consuming chlorinated drinking water were further grouped according to duration of consumption. Three a priori defined exposure categories were used: no/low exposure group (reference category) including subjects not drinking chlorinated drinking water or consuming chlorinated drinking water for short time periods; an intermediate exposure group, corresponding in most studies to a consumption of chlorinated drinking water from 1 to 40

Table 2 Odds ratios and 95% confidence intervals from the studies included in the meta-analysis according to duration of exposure to chlorinated drinking water

Case-control studies					
Cantor 98	Never exposed	1–19 years	20–39 years	40–59 years	⩾60 years
Men	1.0	1.1 (0.8 to 1.3)	1.3 (0.9 to 1.8)	1.5 (0.95 to 2.3)	1.9 (1.1 to 3.6)
Women	1.0	0.9 (0.6 to 1.4)	0.7 (0.3 to 1.3)	0.7 (0.3 to 1.4)	0.7 (0.2 to 2.4)
Both sexes	1.0	1.0 (0.8 to 1.2)	1.1 (0.8 to 1.4)	1.2 (0.8 to 1.7)	1.5 (0.9 to 2.6)
Koivusalo 98	<15 years	15–29 years	30–44 years	⩾45 years	
Men	1.0	1.07 (0.73 to 1.55)	1.67 (1.01 to 2.78)	2.32 (0.99 to 5.45)	
Women	1.0	0.92 (0.49 to 1.72)	1.19 (0.53 to 2.64)	1.88 (0.54 to 6.57)	
Both sexes*		1.03 (0.74 to 1.42)	1.52 (1.0 to 2.33)	2.2 (1.1 to 4.4)	
King 96	⩽9 years	10–19 years	20–34 years	⩾35 years	
Men	–	–	–	–	
Women	–	–	–	–	
Both sexes	1.0	1.04 (0.71 to 1.53)	1.15 (0.86 to 1.51)	1.41 (1.09 to 1.81)	
McGeehin 93	0 years	1–10 years	11–20 years	21–30 years	>30 years
Men	–	–	–	–	–
Women	–	–	–	–	–
Both sexes	1.0	0.7 (0.4 to 1.3)	1.4 (0.8 to 2.5)	1.5 (0.8 to 2.9)	1.8 (1.1 to 2.9)
Vena 93†	0–49 years	50–59 years	60–67 years	68–86 years	
Men	2.89 (1.47 to 5.67)	1.85 (0.96 to 3.57)	2.27 (1.14 to 4.50)	2.24 (1.05 to 4.74)	
Women	–	–	–	–	
Both sexes	–	–	–	–	
Cantor 87‡	0 years	1–19 years	20–39 years	40–59 years	⩾60 years
Men	1.0	1.1 (0.7 to 1.6)	1.1 (0.7 to 1.5)	1.2 (0.8 to 1.7)	1.2 (0.7 to 2.1)
Women	1.0	1.8 (0.8 to 3.7)	1.5 (0.7 to 3.1)	2.2 (1.0 to 4.8)	3.2 (1.2 to 8.7)
Both sexes	1.0	1.2 (0.9 to 1.7)	1.1 (0.8 to 1.6)	1.3 (0.9 to 1.9)	1.4 (0.9 to 2.3)
Cohort studies					
Doyle 97	100% ground water	Mixed ground-surface water	100% surface water		
Women	1.0	2.27 (1.2 to 4.31)	0.62 (0.15 to 2.63)		
Wilkins and Comstock 81	Deep well users	Chlorinated surface water users			
Men	1.0	1.80 (0.8 to 4.75)			
Women	1.0	1.60 (0.54 to 6.32)			
Both sexes*		1.7 (0.8 to 3.5)			

*Risk for both sexes obtained from a meta-analysis of men and women risk. †OR for the quartile of ⩾10 daily cups of tap water consumption. ‡OR for the stratum of water consumption above the population median (1.4 litres).

years; and a high exposure group corresponding in most studies to a consumption of chlorinated drinking water of more than 40 years. In the cohort studies information was provided only on water source and data from these studies are therefore not included in the analysis by duration. When the risk estimates of the intermediate and long term exposure categories we defined did not coincide with the published data, a meta-analysis of risk estimates collapsing exposure categories within study was performed. The cut off points used to define the exposure groups were study specific and did not coincide in all studies (table 1). The influence of the cut off points in determining results was examined in alternative analyses. Potential sources of heterogeneity were examined through graphical methods such as the Galbraith plot.[23] A heterogeneity test based on the Q statistic, following a χ^2 distribution, was performed in all meta-analysis. We considered that there was statistically significant heterogeneity when p value was below 0.10.[22] In cases with substantial heterogeneity random effects models were applied.[22]

The influence of each single study on the combined risk estimate was further examined by consecutively omitting each study from the meta-analysis.[24] Meta-regression was implemented to explain potential heterogeneity attributable to study design and year of publication,[25] fitting random effects models with two additive variance components (within and between studies).[22 26]

Under the assumptions of linear dose-response and independence of the dose specific OR, we estimated the dose-response regression slopes of each study for both sexes, using the OR, 95% confidence intervals and the midpoint of the exposure interval.[27] For open ended intervals a point 20% higher than the low end of the interval was used.[27] We then performed a meta-analysis of the slopes and their standard errors to get a combined dose-response slope for all the studies. The exponentiation of the slope gave the OR for a unit increase of the exposure index (one year of exposure). To overcome the problem of assuming independence of dose specific OR (which is incorrect as they have a common reference group), we adjusted the standard error of the within study slopes estimating the covariance. We applied the method previously described by Greenland and Longnecker[28] for the three studies reporting number of cases and controls by exposure category. We checked for publication bias through Egger's and Begg's graphical methods.[29 30] Analyses were done using Stata v6.0.

RESULTS

All selected studies reported excess risks of bladder cancer ranging from 1.4 to 2.2 for the study specific highest exposure category in both sexes combined (table 2) although only in four studies were results statistically significant. In all case-control studies OR tended to increase with duration of exposure.

Ever consumption of chlorinated drinking water was associated with bladder cancer with a combined risk estimate of 1.2, (95%CI 1.1 to 1.4) for both sexes, on the basis of six studies (fig 1). Sex specific combined risk estimates were 1.4 (95%CI 1.1 to 1.9) for men on the basis of five studies and 1.2 (95%CI 0.7 to 1.8) for women, on the basis of five studies (table 3).

Results from the meta-analysis show a statistically significant increased risk for bladder cancer, associated to long term exposure to chlorinated drinking water (table 3). The combined risk estimate for both sexes and the mid-term exposure was 1.1 (95% CI 1.0 to 1.2) on the basis of five studies. The combined risk estimate for the long term exposure was 1.4 (95%CI 1.2 to 1.7) on the basis of five studies. Combined risk estimates were slightly lower in women (combined OR=1.4) for the long term exposure category, compared with men (combined OR=1.6) (table 3). Inclusion of the

Table 3 Combined risk estimates from studies on bladder cancer and consumption of chlorinated drinking water by sex and exposure category

Exposure category	Meta-OR (95% CI)	Number of studies	Test for heterogeneity p value	Selected method
Both sexes				
Mid-term	1.1 (1.0 to 1.2)	5	0.84	Fixed effects
Long term	1.4 (1.2 to 1.7)	5	0.55	Fixed effects
Ever exposed	1.2 (1.1 to 1.4)	6*	0.61	Fixed effects
Men				
Mid-term	1.3 (1.0 to 1.7)	4	0.08	Random effects
Long term	1.6 (1.2 to 2.2)	4	0.11	Random effects
Ever exposed	1.4 (1.1 to 1.9)	5*	0.01	Random effects
Women				
Mid-term	1.0 (0.7 to 1.6)	3	0.09	Random effects
Long term	1.4 (0.6 to 3.6)	3	0.01	Random effects
Ever exposed	1.2 (0.7 to 1.8)	5*	0.01	Random effects

*Includes the cohort studies that do not provide risk estimates by duration of consumption.

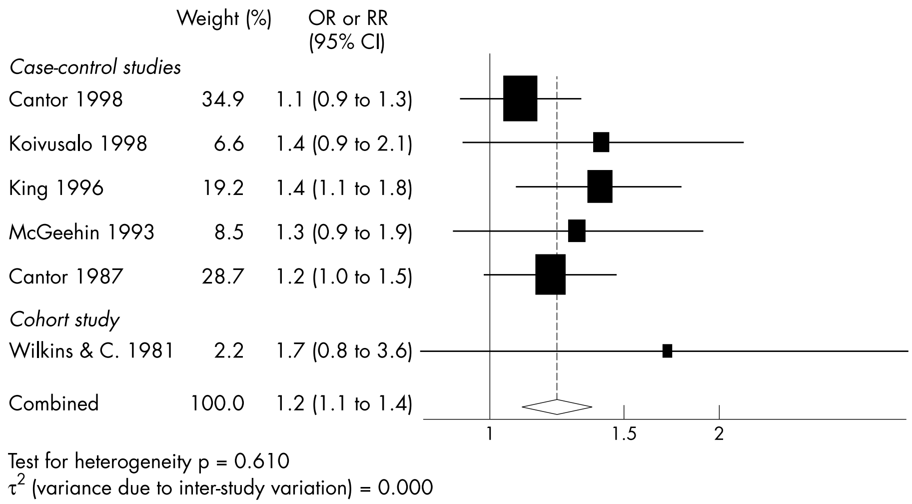

Figure 1 Odds ratios (OR), 95% confidence intervals (95% CI), study weight in the meta-analysis and combined risk estimate from meta-analysis of studies on bladder cancer and ever consumption of chlorinated drinking water. Both sexes.

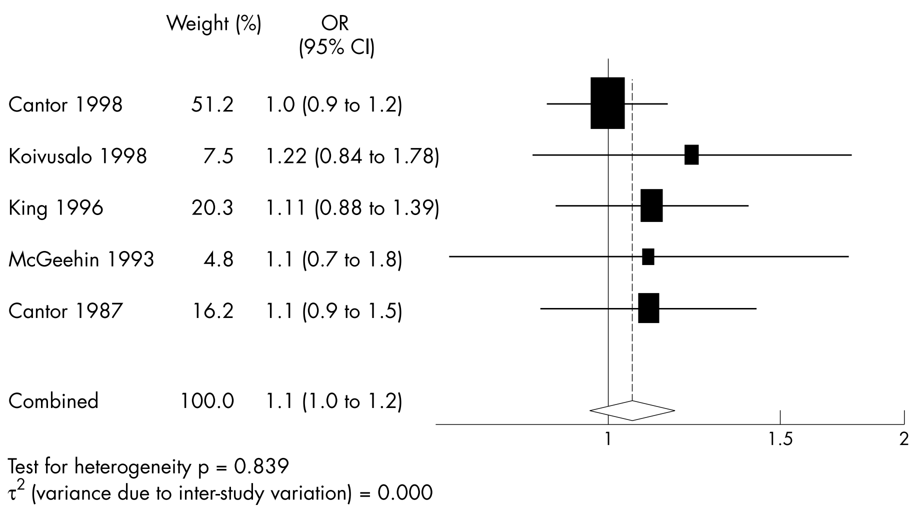

Figure 2 Odds ratios (OR), 95% confidence intervals (95% CI), study weight in the meta-analysis and combined risk estimates from meta-analysis of case control studies on bladder cancer and mid-term consumption of chlorinated drinking water. Both sexes.

cohort study or, alternatively, of the nested case-control study by Freedman *et al*, modified minimally the results. The combined OR for both sexes and long term exposure category was 1.5 (95% CI 1.3 to 1.7) when including the cohort study by Wilkins and Comstock, and the combined OR was 1.4 (95% CI 1.2 to 1.6) when including the nested case-control study.

The study specific OR for both genders and the mid-term and long term exposure categories are shown in figures 2 and 3, respectively. OR for the long term exposure category are comparable and both the test for heterogeneity and the Galbraith plot, which is a more sensitive method than the χ^2 statistic, do not indicate substantial differences between studies (fig 4 and 5). Heterogeneity of results among studies is,

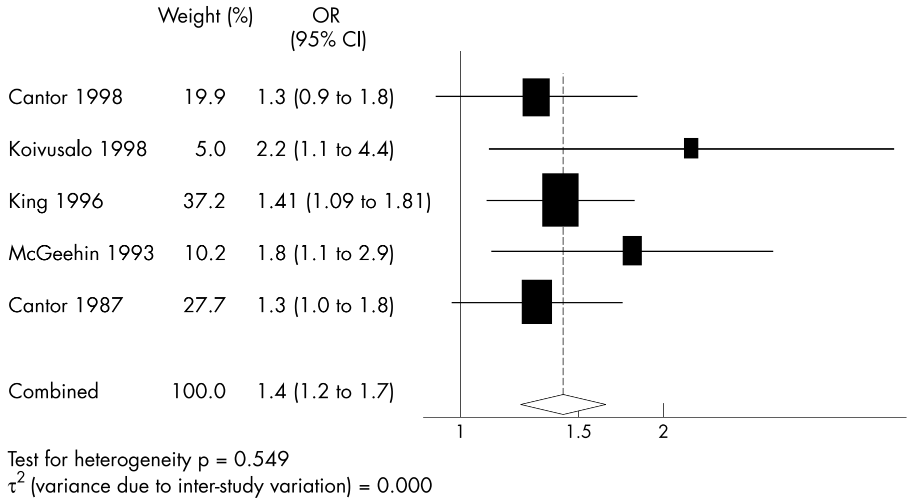

Figure 3 Odds ratios (OR), 95% confidence intervals (95% CI), study weight in the meta-analysis and combined risk estimate from meta-analysis of case-control studies on bladder cancer and long term consumption of chlorinated drinking water. Both sexes.

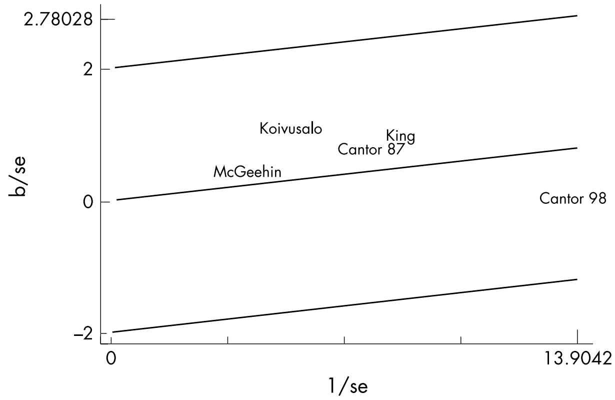

Figure 4 Galbraith plot for mid-term exposure, both sexes. The Galbraith plot provides a graphical display to get a visual impression of the amount of heterogeneity from a meta-analysis. For each study, the z statistic (*β/s.e._β*) is plotted against the reciprocal standard error *1/s.e._β*. The (unweighted) regression line constrained through the origin, with its 95% confidence interval, has a slope equal to the overall log odds ratio in a fixed effects meta-analysis. The position of each study on the horizontal axis gives an indication of the weight allocated to it in a meta-analysis. The position on the vertical axis gives the contribution of each study to the Q statistic for heterogeneity. In the absence of heterogeneity we could expect all the points to lie within the confidence bounds (positioned two units over and below the regression line).

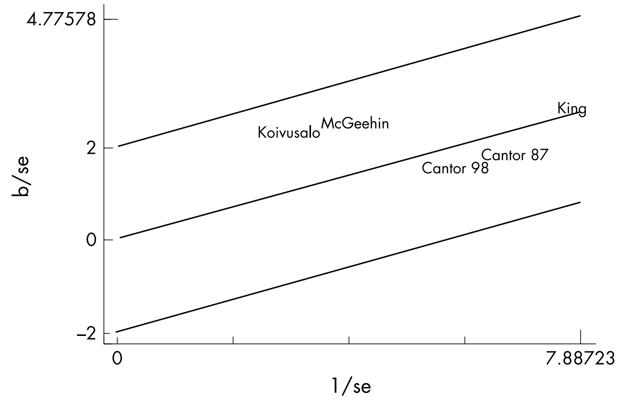

Figure 5 Galbraith plot for long term exposure, both sexes. (See legend to figure 4 for explanation of the Galbraith plot).

however, particularly evident for results in women that are based on three studies and on comparatively small numbers (table 3). In men, the main source of heterogeneity was attributable to the inclusion of the study by Vena,[15] particularly for mid-term exposure. Excluding this study resulted to an OR for men in the mid-term exposure category of 1.2 (95%CI 1.0 to 1.4) and p value for heterogeneity of 0.82. We explored through meta-regression whether year of publication was associated with the magnitude of the OR but found no statistically significant effect attributable to the year of publication for either of the two exposure categories.

We evaluated whether the cut off points selected could influence results, and calculated combined OR for two a priori defined "alternative" intermediate and high exposure categories. We selected as "alternative" intermediate exposure group the most comparable exposure category among studies, which corresponded to the strata including 25–26 years of consumption of chlorinated drinking water (table 2). The combined OR for this group was 1.2 (95% CI 1.0 to 1.4) with a p value for a test of heterogeneity of 0.36. The "alternative" high exposure group included the highest exposure strata in each study. The meta-OR for this group was 1.6 (95% CI 1.3 to 1.8) with a p value for a test of heterogeneity of 0.79. Similar to the overall combined OR, the gender specific combined OR calculated on the basis of these "alternative" exposure categories were slightly higher than those shown in table 3, and results for these categories were less heterogeneous.

The study by Cantor *et al*, 1987[13] reports OR by quantity of tap water consumption stratified below or above the median population level of daily water consumption (1.4 litres). Our model includes the OR of the most exposed stratum, tap water consumption above the median. We explored the effect on the combined risk estimate considering the OR from the stratum below the median. The risk estimate changed little for the overall combined risk estimate (OR=1.4, 95%CI 1.2 to 1.7); test for heterogeneity p value=0.528).

The study by Doyle reports results for three types of water source: subjects consuming 100% surface water (highest exposure), those consuming mixed surface and ground water, and those consuming 100% ground water (non-exposed). We included in our model the highest exposure category that included, however, only few subjects. We also checked for the effect on the results when using the intermediate exposure category that included the most exposed subjects. When using the intermediate category in the combined analysis, the OR increased (OR=1.4, 95%CI=0.9 to 2.2, test for heterogeneity=0.02).

Table 4 Dose-response regression slopes obtained from weighted least squares within study, and combined odds ratios (OR) with 95% confidence intervals (95% CI) obtained from the meta-analysis of the five slopes and their standard errors. Both sexes

Study	Slope	Standard Error	OR	(95% CI)
Cantor 1998	0.0039614	0.0021449		
Koivusalo 1998	0.0098449	0.003775		
King 1996	0.0072381	0.0025664		
McGeehin 1993	0.0159266	0.0057087		
Cantor 1987	0.0049595	0.0024032		
Combined				
unit increase	0.006	0.000128	1.006	1.004 to 1.009
20 years			1.13	1.08 to 1.20
40 years			1.27	1.17 to 1.43
60 years			1.43	1.27 to 1.72

Four studies applied elaborate exposure models and estimated long term level of exposure to trihalomethanes [9 10]or to water mutagenicity attributable to the presence of chlorination byproducts.[8] Risk estimates in the three studies examining both sexes were 1.4,[10] 1.5,[9] and 2.2[8] for long term exposure. The combined risk estimate for these three studies was 1.5 (95% CI 1.2 to 1.8) with a p value for the test of heterogeneity of 0.61.

The results of the dose-response analysis are shown in table 4. The combined OR for unit increase in duration of exposure is 1.006 (95%CI 1.004 to 1.009). For 20, 40, and 60 years of exposure, combined OR are respectively 1.13 (95%CI 1.08 to 1.20), 1.27 (95%CI 1.17 to 1.43), and 1.43 (95%CI 1.27 to 1.72). The comparison of "crude" and "adjusted" combined OR for the three studies that permitted the calculation of a covariance matrix, showed that adjusting for covariance led to a 20% lower combined estimate. For these three studies, the combined OR for unadjusted slopes was 1.005 per year of exposure (95%CI 1.003 to 1.008), standard error (SE)=0.00128. After adjusting for covariance, the combined OR was 1.004 (95%CI 1.001 to 1.007), SE=0.00153.

We found no evidence of publication bias. Egger's graph showed a slight negative slope indicating that the smaller and less precise studies tended to report higher risk estimates, while the bigger and more precise studies tended to report lower risk estimates. However, the evidence of this trend is not statistically significant. We performed also the Begg's and Egger's tests to check for publication bias in the models stratified by sex. Because of the small number of studies, the test is not reliable as the confidence intervals very wide.

DISCUSSION

Results of this meta-analysis indicate the presence of a moderate excess risk for bladder cancer attributable to consumption of chlorinated drinking water. A clear excess risk was observed among subjects consuming chlorinated drinking water for more than about 40 years. The risk estimate for the intermediate exposure category was only slightly increased, though it also was statistically significant. Overall, results for long term exposure to chlorinated drinking water were consistent between studies and fairly consistent exposure-response patterns were observed in all case-control studies. Previous meta-analyses or reviews[31] had reached the same conclusions but either did not provide a quantitative summary of the effect, or did not base the analyses and conclusions on those studies with individual information.

Exposure assessment has been identified as one of the main problems when evaluating results of epidemiological studies on chlorination by products[32] and recent studies have made considerable efforts in characterising lifetime exposure. All studies included in this meta-analysis recorded individual information on water consumption. Heterogeneity of the methods used in different studies and different background levels of chlorination byproducts remains, however, a main concern. Statistical heterogeneity of the results was present for the intermediate exposure category and particularly for results stratified by gender. Small numbers, especially in women, and differences in exposure assessment are probably the most important sources of heterogeneity of results between studies. The study by Vena *et al*[15] was the main source of statistical heterogeneity observed particularly in the mid-term category. In this study, OR were generally higher than in other studies, and is the least comparable to the other studies concerning various aspects of assessment of exposure including the exposure categories used.

The exposure categories used in the meta-analysis could correspond to different levels of exposure to chlorination byproducts between studies. The exposure strata used were not directly comparable between studies and also, levels of chlorination byproducts would be expected to differ between the geographical areas examined in these studies. Despite our effort to select the most comparable exposure categories identifying subjects with intermediate and long term consumption of chlorinated drinking water, exposure categories between studies differed. Even though the highly exposed group included in all studies subjects with long term consumption of chlorinated water the cut off points differed between studies. In one study the minimum was 30 years, in another 35 years, in two studies 40, in one study 45, and in two 50 years. More importantly, the groups considered as non-exposed in two studies had consumed chlorinated drinking water for a few years, which would have led to an underestimation of the risk. In an alternative analysis we examined the extent to which the definition of the cut off points could affect results. This analysis indicated that observed results are robust. Even though different estimates can be derived if the data are categorised in alternative ways, these differences are small and results tend to support a positive association between consumption of chlorination drinking water and bladder cancer.

Levels of trihalomethanes were measured and modelled only in three studies [9 10 16a] while a fourth study used a matrix of water mutagenicity that corresponds well with levels of chlorination byproducts.[8] In the two studies measuring trihalomethanes and evaluated both sexes, risks for specific contaminant levels were comparable. The extent to which this finding can be extrapolated to the other studies included in this analysis is unknown and, in principle, one should not expect that risks by duration of exposure should be directly comparable as levels of contaminants and type of contaminants differ between areas and time periods. It should be noted that trihalomethanes have been traditionally used as markers of the whole mixture of chlorination byproducts because they are the most prevalent byproducts. Other chlorination byproducts such as haloacetic acids and MX, have also been shown to have mutagenic or carcinogenic properties.[33–35]

In one study the excess risk identified was present only among ever smokers.[9] All studies adjusted for important confounding factors like age, sex, and smoking and some studies also for occupation and socioeconomic status. Residual confounding attributable to smoking could still be present but, overall, confounding seems to be an unlikely explanation for the findings of individual studies and the results of the meta-analysis.

The alternative dose-response methods we used confirmed the existence of an excess risk, though they led to combined risk estimates of slightly different magnitude. According to the dose-response analysis described by Berlin[27] and Greenland,[28] we reached combined risk estimates slightly lower than according our intermediate term and long term exposure approach. The combined risk estimates obtained from both methods are comparable for the intermediate duration of exposure (about 20 years), and the difference seems to be larger for long term exposures. Both methodologies have their limitations. The dose-response slope approach is based on the assumption of a linear dose-response, which may be a simplification of the real dose-response trend. The mid-term, long term approach implies the combination of risk estimates from exposure categories that are not fully comparable among studies. These results obtained from different methodologies indicate the presence of an excess bladder cancer risk associated with exposure to disinfection byproducts, and also indicate that the limitations of each method are probably not producing a spurious association.

Publication bias is a concern for all meta-analyses. Our bibliographic search was limited to databases including published studies. There may exist other not published studies, for example, doctoral theses and congress communications. It is extremely difficult to identify such studies. Furthermore, their inclusion could be questioned as quality criteria are difficult to apply. A simple observation of the graphics presented (figs 1–3) indicates that there is no trend along the years. If publication bias did exist, reported risks would tend to be higher in the first published studies, and lower risks in more recent. We additionally examined with publication bias through statistical and graphical methods, showing no evidence of such bias.

To conclude whether disinfection byproducts (DBP) or chlorinated drinking water exposure is a risk factor for certain cancers, evaluations could be based on an evaluation of single compounds but should also be based on the effect of the total DBP mixture, as humans are exposed to complex mixtures of DBP and it is impossible to evaluate the effect of one single compound through epidemiological studies. Results of this meta-analysis of case-control studies of bladder cancer and chlorinated drinking water exposure provide an objective summary risk for one of the cancers most consistently associated to DBP exposure.

In industrialised countries disinfection and chemical protection of drinking waters should not be considered as antagonistic. The recommendations of a recent report by the WHO[3] similar to previous reports although applicable at a global level, do not correspond to the current situation of most industrialised societies where contamination of the water by microorganisms has been drastically, although not entirely,[36] reduced. Traditional drinking water treatment is highly chlorine and chemical based. There exist reasonable alternatives that keep the disinfection power and produce fewer byproducts. In the long term, the most efficient approach is the protection of source waters aimed at reducing the presence of natural organic matter.[3] Exposure to chlorination byproducts occurs through ingestion, inhalation, and dermal absorption.[37–39] Epidemiological studies have only evaluated ingestion. Changing drinking water practices, for example consuming bottled water, would reduce exposure to trihalomethanes by only about one third.[38]

In conclusion, on the basis of epidemiological evidence, chronic exposure to chlorinated drinking water is associated with a moderate increased risk for bladder cancer, particularly among men. The estimated relative risks are not high, but the population attributable risk could be important, as the vast majority of the population of industrialised countries is potentially exposed for long time periods.

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